REMARKS

1. Formal Matters

a. Status of the Claims

Claims 21-23 and 33-35 are pending in this application. Claims 21-23 are amended, and claims 45-47 are new. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the instant application. Upon entry of this amendment, claims 21-23, 33-35, and 45-47 are pending and under active consideration.

b. Amendments to the Claims

Support for the amended claims can be found in the application as originally filed as described in Table A.

Table A

Claim	Support
21	paragraphs 0018, 30618, and 30619, and Table, lines 15221-15225
22	paragraphs 0018 and 30620, and Table 1, lines 15221-15225
23	as described for amended claim 22 and Table 2, lines 151383-151482
45	as described for amended claim 21 and paragraph 0011
46	as described for amended claim 22 and paragraph 0011
47	as described for amended claim 23 and paragraph 0011

c. Amendments to the Specification

Support for the amendments to the specification can found at Figures 12-14 as originally filed.

d. Sequence Compliance

On pages 2 and 3 of the Office Action, the Examiner objects to the Specification and Drawings for failing to comply with the requirements of 37 C.F.R. § 1.821-1.825. The Examiner asserts that Figures 12-14 of the Drawings contain nucleic acid sequences, but neither the Figure nor the Description of the Figures identifies the sequences with an appropriate sequence identifier. Applicant respectfully submits that the Amendments to the Specification requested hereinabove assign sequence identifiers to the sequences shown in Figures 12-14 by identifying the appropriate SEQ ID NOs in the Brief Description of Drawings in compliance with 37 C.F.R. § 1.821-1.825.

On page 3 of the Office Action, the Examiner requests that Applicant return a copy of the Notice to Comply mailed with the Office Action. The assigned sequence identifiers described above refer to sequences included in the Amended Sequence Listing submitted on compact disc on September 25, 2006 and entered on September 27, 2006. Accordingly, no new sequence listing is required. In view of the

foregoing, Applicant is returning a copy of the Notice to Comply mailed with the Office Action, but is not submitting a Sequence Listing.

2. Patentability Remarks

a. 35 U.S.C. § 112, Second Paragraph

On page 3 of the Office Action, the Examiner rejects claims 21-23 and 33-35 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite due to the limitation "≥24 consecutive nucleotides of SEQ ID NO: 5264" of claim 21. The amended claims no longer recite this limitation, thereby rendering this rejection moot. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 21-23 and 33-35 under 35 U.S.C. § 112, second paragraph.

b. 35 U.S.C. § 112, First Paragraph

On pages 4-6 of the Office Action, the Examiner rejects claims 21-23 and 33-35 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claim 21, "wherein Y≥24"

On page 5 of the Office Action, the Examiner asserts that claim 21 contains new matter due to the limitation "≥24 nucleotides of SEQ ID NO: 5264." The amended claims no longer recite this limitation, thereby rendering this rejection moot.

Claim 21, "at least 73.7% identical to" nucleotides 51-69 of SEQ ID NO: 2194

On pages 5 and 6 of the Office Action, the Examiner asserts that the disclosure does not support the limitation "at least 73.7% identical to nucleotides 51-69 of SEQ ID NO: 2194." Amended claim 23 is related to a sequence at least 77.3% identical to SEQ ID NO: 5264, a miRNA formed by the hairpin with SEQ ID NO: 2194 (which is GAM2191). On page 5 of the Office Action, the Examiner notes that Table 2 discloses that a miRNA formed by SEQ ID NO: 2194 can bind to the target gene YWHAZ with 14 out of 19, or 73.7%, complementary bases. As shown below, Table 2 likewise discloses that the miRNA with SEQ ID NO: 5264 can bind the target gene SF3B3 with 17/22, or 77.3%, complementary bases.

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GENE     TARGET    UTR SEQUENCE                SEQID   BINDING-SITE
======== ========= === ======================= ======= ============================
GAM2191  SF3B3     3'  TCTGGTTAGATTCTAGAGC      29681            CCAGA   _
                                                        TCTGGTTAGA     TCT GAGC
                                                        ||||||||||     ||| ||||
                                                        AGACCAATCT     AGA CTCG
                                                                  A____   T
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Furthermore, paragraph 0014 of the specification describes that miRNAs can bind target genes with less than 100% complementarity: "a nucleotide sequence of the RNA encoded by the novel viral gene is a partial inversed-reversed sequence of a nucleotide sequence of a binding site associated with at least one host target gene." In view of the foregoing, Applicant submits that one of skill would have understood

that 77.3% complementarity is sufficient for a miRNA to bind a target mRNA. Accordingly, one of skill in the art would have understood that a nucleic acid at least 77.3% identical to SEQ ID NO: 2194 is capable of binding target mRNAs.

Claim 21, "18 to 120" (maintained rejection)

On pages 6 and 7 of the Office Action, the Examiner maintains the rejection of claims 21-23 and 33-35 under 35 U.S.C. § 112, first paragraph, because there is no support in the specification as originally filed for an isolated nucleic acid of 18 to 120 nucleotides in length. The amended claims no longer recite this limitation, thereby rendering this rejection moot. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 21-23 and 33-35 under 35 U.S.C. § 112, first paragraph.

c. 35 U.S.C. § 101

On pages 7-17 of the Office Action, the Examiner maintains the rejection of claims 21-23 and 33-35 under 35 U.S.C. §101, for allegedly lacking utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher* 421 F.3d 1365, 1371 (2006) and *Revised Interim Utility Guideline Training Materials* ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See In re Fisher* 421 F.3d at 1371 and Guidelines. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The Fisher application did not disclose the location of the ESTs in the genome or the function of the underlying genes. Fisher asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Id.* at 1367 and 1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids maybe used to target and modulate expression of **specific** gene transcripts. Table 2, lines 35,003-35,007 of the specification disclose that the **claimed microRNA-related sequences specifically target** mRNA transcripts of the SF3B3 gene. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene SF3B3**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the SF3B3 gene.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See In re Fisher* at 1371 and the Guidelines. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In Fisher, it was admitted that the underlying genes for the ESTs had no known function. Fisher argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, Fisher failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Id.* at 1373 quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of SF3B3. *See* Table 2, lines 151,393-151,397. At the time of filing, it was known in the art that SF3B3[1] is part of the SF3b complex, which is involved in the assembly of the prespliceosome, contributes to the recognition of an intron's branchpoint, and integrates the U2 small nuclear ribonucleotide protein (snRNP) in the catalytically active spliceosomal C complex.

[1] SF3B3 is also referred to in the art as SF3b130, SAP 130, and RSE1.

See MacMillan *et al., Genes Development* 8:3008 (1994), Das *et al., Mol Cel Biol* 19:6796-6802 (1999), and Golas *et al., Science* 300:980-983 (2003). SF3B3 was known be essential for viability in yeast, that the SF3b complex and its components are conserved in eukaryotes, and that the SF3b is absolutely required for pre-mRNA splicing. *See* Das *et al.* and Golas *et al.* RNA splicing is an essential, precisely regulated post-transcriptional process that occurs prior to mRNA translation. Changing splicing may have a dramatic effect on the level of protein expression. It is important that the regulation of RNA splicing is at a comparable level to that observed for RNA transcription or translation. *See* Lopez *et al., Annual Rev. Genet.*32:279-305 (1998).

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. One such benefit is the ability to modulate expression of SF3B3 in order to modulate the level of spliced RNAs. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requires are satisfied in accordance of Fisher and the Guidelines.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely than not true. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix) that the claimed nucleic acids would likely inhibit expression of the SF3B3 mRNA transcript. Dr. Pilpel's opinion is based on a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. See paragraphs 2 and 3 of the Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. See paragraph 3 of the Pilpel Declaration. If there is

insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. See paragraph 3 of the Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. See paragraph 3 of the Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequence as set forth in SEQ ID NO: 5264 and its target gene sequence of SF3B3 (as depicted in Column B, Last Row, Page 5 of Table A) are consistent with the characteristics of the microRNA:target mRNA binding described above. See paragraph 6. In view of these conserved characteristics, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 5264 (Column B, Last Row, Page 5 of Table A) is likely to inhibit expression of the protein encoded by the target gene SF3B3 in view of the characteristics of microRNA:mRNA binding properties. See paragraph 6 of the Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. See paragraph 4 of the Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al., Genome Biology* 5:R1 (2003)) as examples of such algorithms. The TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorigthm; where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. See Paragraph 4 of the Declaration.

Importantly Dr. Pilpel states that SEQ ID NO: 5264 and its target gene sequence of SF3B3 are consistent with microRNA and target mRNAs predicted by the algorithms described above. See paragraphs 4 and 5 of the Pilpel Declaration. Moreover, Dr. Pilpel states that the TargetScan algorithm and miRanda algorithm detects the binding of SEQ ID NO: 5264 to SF3B3. See paragraph 5 of the Pilpel Declaration and Last Row, Page 5 of Table A. In view of these facts, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 5264 is likely to inhibit expression of the protein where co-expressed. See paragraph 6 of the Pilpel Declaration.

(c) SF3B3

Applicant further submits that SF3B3 is a credible target for trans-acting regulatory elements. Specifically, the Pilpel Declaration indicates that the nucleic acid having the sequence as set forth in SEQ ID NO: 5264 has been biologically validated. See Column B, Last Row, Page 5 of Table A. Accordingly, SF3B3 is an important target in nature by trans-acting elements such as microRNAs.

In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of SF3B3, which in turn would modulate the level of spliced mRNAs. Accordingly, a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §101.

d. 35 U.S.C. § 112, first paragraph

On page 17 of the Office Action, the Examiner asserts that because the claimed subject matter lacks credible, specific, and substantial utility, the specification also does not provide an enabling disclosure. Applicant disagrees. In view of the claimed subject matter having credible, specific, and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: January 25, 2008

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